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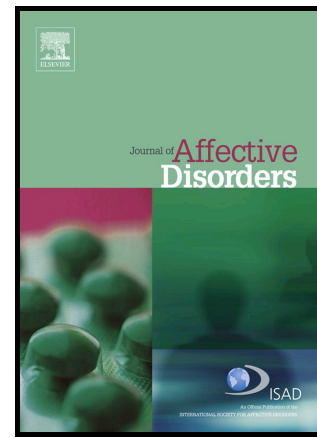
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ACETYLCHOLINESTERASE INHIBITORS AND MEMANTINE IN BIPOLAR DISORDER: A
SYSTEMATIC REVIEW AND BEST EVIDENCE SYNTHESIS OF THE EFFICACY AND SAFETY FOR
MULTIPLE DISEASE DIMENSIONS

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ABSTRACT

Background

Acetylcholinesterase inhibitors (AceI) and memantine might prove useful in bipolar disorder (BD) given their neuroprotective and pro-cognitive effects, as highlighted by several case reports. We aimed to systematically review the efficacy and safety of AceI and memantine across multiple outcome dimensions in BD.

Methods

Systematic PubMed and SCOPUS search until 04/17/2015 without language restrictions. Included were randomized controlled trials (RCTs), open label studies and case series of AceI or memantine in BD patients reporting quantitative data on depression, mania, psychotic symptoms, global functioning, or cognitive performance. We summarized results using a best-evidence based synthesis.

Results

Out of 214 hits, 12 studies (RCTs=5, other designs=7, total n=422) were included. Donepezil (studies=5; treated=102 vs. placebo=21): there was strong evidence for no effect on mania and psychotic symptoms; low evidence indicating no effect on depression. Galantamine (studies=3; treated=21 vs. controls=20) (placebo=10, healthy subjects=10): there was strong evidence for no effect on mania; moderate evidence for no effect on depression; low evidence for no effect on global functioning. Memantine (studies=4; treated=152 vs. placebo=88): there was conflicting evidence regarding efficacy for mania, depression and global functioning.

Limitations

paucity of RCTs; small sample size studies; heterogeneous data and patients characteristics

Conclusion

There is limited but converging evidence of no effect of AceI in BD, and conflicting evidence about memantine in BD. Too few studies of mostly medium/low quality and lacking sufficient numbers of patients in specific mood states, especially mania, contributed data, focusing solely on short-

term/medium-term treatment, necessitating additional high-quality research to yield more definite results.

Keywords: bipolar disorder; acetylcholinesterase inhibitors; memantine; depression; mania; psychosis.

INTRODUCTION

Bipolar disorder (BD) is a chronic mental illness affecting 1-2% of adult population (Weissman et al., 1988), with estimates of up to 4.5% for the spectrum of bipolar disorders (Merikangas et al., 2007). BD seems to be associated with impairments in neurotrophic, cellular plasticity and resilience pathways as well as in neuroprotective processes (Soeiro-de-Souza et al., 2012), supporting the concept that BD is a neurodegenerative disease. However, a precise and specific pathophysiological mechanism underlying BD has not been clarified yet.

Traditional mood stabilizers, namely lithium, carbamazepine and valproate, and antipsychotics are effective for the treatment of acute manic episodes (Cipriani et al., 2013) and for relapse prevention (Miura et al., 2014), while options for bipolar depression are more limited (ME, 2006). Nevertheless, despite approval of these effective medication treatments, unfortunately up to half of patients have an insufficient response to pharmacotherapy (Calabrese and Delucchi, 1990; Freeman et al., 1992; Pope et al., 1991; Small et al., 1991; Swann et al., 1997). Moreover, naturalistic data suggest that patients spend about half of the time ill during the 2 years following a manic index episode (Jann, 2014). These data stress the need to evaluate other pharmacologic agents for the treatment of BD, which may intersect with specific etiologic pathways that are not targetable with available drugs.

Recently, a catecholaminergic-cholinergic hypothesis has been suggested based on neuroimaging, genetic, and psychopharmacological data, indicating increased cholinergic functioning during depressive phases and increased catecholaminergic (particularly, dopaminergic and norepinephrinergic) functioning during manic phases of BD (van Enkhuizen et al., 2015).

Acetylcholinesterase inhibitors (AceI) (donepezil; galantamine; rivastigmine) and memantine, which affect cholinergic transmission among other mechanisms (Drever et al., 2007), are currently used for the treatment of cognitive impairment in Alzheimer's disease (Birks, 2006). Approximately 30-60% of individuals with BD experience a worsening in occupational and social domains after an initial remission of their mood disorder (Kam et al., 2011). Furthermore, BD has been associated with cognitive dysfunction (Torres et al., 2007). Data in older people with BD showing worse information processing speed and executive functioning than age-matched controls (Gildengers et al., 2007) could suggest that these individuals are at higher risk of cognitive problems particularly during late-life. In this context, the use of memantine might be appropriate since this drug is commonly used in moderate-severe forms of Alzheimer's disease and seems to have neuroprotective effects (Lopes et al., 2013). Moreover, based on uncontrolled observations and case reports, memantine seems to also have potential anti-manic and mood stabilizing effects (Serra et al., 2014c) making it an interesting intervention for BD.

Until now, evidence suggests use of donepezil in schizophrenia yields no effect (Keefe et al., 2008), while galantamine seems to improve some cognitive domains (Buchanan et al., 2008; Lee et al., 2007; Schubert et al., 2006), particularly in combination with antipsychotics; however evidence is still weak due to the limitations of included studies (Singh et al., 2012). Similarly, a systematic review (Zdanys and Tampi, 2008) did not find conclusive results for the use of memantine in several psychiatric disorders, including depression, schizophrenia, obsessive-compulsive disorder, substance abuse, pervasive developmental disorders, and binge eating disorder. The same authors found limited evidence for memantine in BD although this conclusion was limited to findings from case-reports (Zdanys and Tampi, 2008).

With regards to mood symptoms, AceI could theoretically be promising, particularly during manic phases. As shown from the beginning of 1900, increased cholinergic tone may have a depressant effect on mood in mania. For example, physostigmine leads to a dramatic effect on mania as initially reported by Janowsky (Janowsky et al., 1972). Newer AceI inhibit the degradation of

acetylcholine in the synapses with lower side effects than physostigmine and could be effective for manic symptoms. Moreover, galantamine could further increase the levels of acetylcholine in the brain through the allosteric modulation of $\alpha_4\beta_2$ and α_7 nicotinic receptor, indirectly increasing dopamine and glutamate levels (Samochocki et al., 2003).

In order to test the clinical relevance of these aforementioned pharmacologic considerations and results, we conducted a systematic review of studies including patients with BD treated with Acel and memantine, investigating their effect on depression, mania, global functioning, cognitive performance, psychotic symptoms and relapse prevention.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al, 2009).

Search Strategy

Two investigators (N.V., M.S.) independently conducted an electronic literature search using PubMed and Scopus, without language restriction, from database inception until 04/17/2015, for clinical studies investigating the effect of Acel and memantine in patients with BD. Any inconsistencies were resolved by consensus. In PubMed, controlled vocabulary terms (MeSH and the following keywords were used) and the following keywords were used: ((bipolar OR mania OR manic) AND ("donepezil" OR "galantamine" OR "rivastigmine" OR "cholinesterase inhibitors" OR "memantine" OR "acetylcholinesterase inhibitors")). Conference abstracts were also considered; at least 4 attempts were made to contact study authors for additional information. Reference lists of included articles and those relevant to the topic were hand-searched for identification of additional, potentially relevant articles.

Study Selection

We included (1) randomized controlled trials (RCTs), open label studies and case series (2) reporting data on AceI or memantine (3) in patients with a clinical or research diagnosis of BD, (4) reporting quantitative data using a validated rating scale to measure symptoms of depression, mania, global functioning, cognitive performance, or psychotic symptoms.

The following studies were excluded: (1) case reports, (2) lacking data about outcome measures, (3) animal or in vitro research, and (4) studies investigating the effect of AceI or memantine with concomitant electroconvulsive therapy (ECT).

Data Extraction

Two authors (N.V., C.L.) independently extracted data from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus. The following information was extracted: i) study population characteristics (e.g., sample size, demographics, presence of comorbidities), ii) design; iii) study duration, iv) clinical setting in which the study was performed, v) inclusion and exclusion criteria, and vi) quantitative data on depression, mania, global functioning, cognitive performance, psychotic symptoms and adverse effects.

Study quality

The quality of involved studies in this systematic review was evaluated using Jadad scale (Jadad et al., 1996). This scale includes randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). The overall score of a study according to this scale ranges from 0–5, with higher scores indicating better quality (Jadad, 2009). Studies with Jadad scores of 0, 1, 2 and ≥ 3 were considered as no, low-, medium- and high-quality, respectively.

Statistical Analysis

The outcomes were the change from baseline to follow-up of rating scale scores measuring depression, mania, global functioning, cognitive performance, and psychotic symptoms as well as the incidence and number of adverse effects.

Due to the limited number of RCTs for each drug and high heterogeneity of the measured outcomes, we summarized the findings of this systematic review using evidence levels instead of using the initially intended meta-analytic approach. Based on prior recommendations (Cao et al., 2013), we used the following grading system. Strong evidence: 2 high-quality studies in agreement about an outcome; moderate: 1 high-quality + 1 medium quality, or 3 medium-quality studies in agreement; low: 1 high quality, or 2 medium-quality, or 3 low studies in agreement; no evidence: 1 medium-quality study, or < 3 studies of low quality studies, or any number of no quality studies in agreement, or no studies at all; conflicting: contrasting findings of low to strong evidence among studies.

INSERT FIGURE 1 HERE

RESULTS

The search identified 430 potentially eligible studies, of which 216 duplicates were excluded. After excluding 198 manuscripts through title and abstract review, 16 full text articles were examined. Altogether, 12 studies were included in the systematic review (**Figure 1**).

INSERT TABLE 1 HERE

Study and Patient Characteristics

Studies and patients characteristics are summarized in **Table 1**. The 12 included studies (Ae et al., 2006; Anand et al., 2012; Burt et al., 1999; Chen et al., 2013; Ghaemi et al., 2009; Gildengers et al., 2008; Iosifescu et al., 2009; Keck et al., 2009; Koukopoulos et al., 2012; Lee et al., 2014; Schrauwen and Ghaemi, 2006) included a total of 434 participants (treated=275, controls=147) for

an average follow-up period of 20 weeks. All studies focused on the short- or medium-term treatment and none reported results on relapse prevention. Nine studies were conducted in the USA (Ae et al., 2006; Anand et al., 2012; Burt et al., 1999; Ghaemi et al., 2009; Gildengers et al., 2008; Iosifescu et al., 2009; Keck et al., 2009; Kelly, 2008a; Schrauwen and Ghaemi, 2006), 2 in Asia (Chen et al., 2013; Lee et al., 2014) and one in Europe (Koukopoulos et al., 2012). Five studies were RCTs, 2 naturalistic case series, 2 retrospective case series, 2 open label trials without a control group and 1 with a control group. Eight studies included out-patients, 4 only in-patients, and 1 patients from both settings. Three studies reported that no patients had an active diagnosis of psychosis, while this information was not available in the other 9 studies (**Table 1**).

Participants treated with AceI or memantine had a mean age of 41.8 ± 16.1 years compared to 36.1 ± 13.9 years in the control group. In the treatment groups, 57.5% of patients were females, compared with 55% of the control subjects (**Table 1**).

Five studies (Ae et al., 2006; Burt et al., 1999; Chen et al., 2013; Gildengers et al., 2008; Keck et al., 2009) explored the effect of donepezil in BD (treated=102; controls=21, all placebo), of which 2 were RCTs (Ae et al., 2006; Chen et al., 2013). Three studies (Ghaemi et al., 2009; Iosifescu et al., 2009; Schrauwen and Ghaemi, 2006) explored the effect of galantamine (treated=21; controls: 20, 10 placebo and 10 healthy subjects), one was a RCT (Ghaemi et al., 2009). Four studies (Anand et al., 2012; Keck et al., 2009; Koukopoulos et al., 2012; Lee et al., 2014) investigated the use of memantine (treated=152; controls=88, all placebo) with 2 studies (Anand et al., 2012; Lee et al., 2014) with a RCT design. No study investigated rivastigmine effects in BD.

Methodological quality of included studies

Quality assessed with the Jadad scale (**Table 1; eTable 1**) indicated that 4 studies (Burt et al., 1999; Keck et al., 2009; Kelly, 2008b; Schrauwen and Ghaemi, 2006) had no quality (Jadad's scale=0), 4 (Gildengers et al., 2008; Iosifescu et al., 2009; Keck et al., 2009; Koukopoulos et al., 2012) had low

quality (Jadad's scale=1), 1 (Iosifescu et al., 2009) had medium quality (Jadad's scale=2), and 5 (Ae et al., 2006; Anand et al., 2012; Ghaemi et al., 2009; Lee et al., 2014) were of high quality (Jadad's scale>3). All the studies with high quality were also RCTs, while among the studies with other designs, only 1 (Iosifescu et al., 2009) included a control group, reaching a medium quality.

INSERT TABLE 2 HERE

Donepezil

Among the five studies exploring the effect of donepezil (**Table 2**), the two RCTs included reported a no significant effect of donepezil regarding the investigated outcomes.

Chen et al. showed that in 30 manic patients randomized to donepezil (n=15) or placebo (n=15) donepezil did not significantly improve manic or psychotic symptoms compared to placebo, while 19 mild to moderate side effects in the donepezil group compared with 7 in the control group were reported (Chen et al., 2013). Similar findings about mania, psychosis, and depression were shown in a RCT involving 11 manic patients (6 treated vs. 5 placebo), although 60% of participants included in the placebo group experienced an almost significant improvement in mania. Altogether, 33 side effects were reported with donepezil, and 7 in placebo group. There was poor compliance in 4 out of 6 patients in the donepezil group and one serious adverse effect occurred in one patient (ultra-rapid cycling) (Ae et al., 2006).

Among the studies with other designs, Burt et al. reported that in a retrospective case series that donepezil led to a mean decrease of CGI-S scores of 1.46 and an increase of GAF scores by 11.5 points in 11 patients with all types of BD. However, the significance of these results was not reported, and neither were data about other possible outcomes. In this study, 5 patients reported a side effect, mainly gastrointestinal in nature (Burt et al., 1999). Gildengers et al. reported data on cognitive function in 12 older euthymic people with BD I and II finding no significant effect of donepezil in cognitive function, and reporting gastrointestinal side effects in 3 of them (Gildengers et al., 2008). Finally, Kelly et al. in a naturalistic case-series of 58 patients with BD reported a

significant improvement in global functioning and cognitive performance in BD-II patients, while the opposite effect was observed in BD-I patients. Seven patients stopped the treatment with donepezil due to side effects (Kelly, 2008a).

Galantamine

Only three studies investigated the effect of galantamine in BD (**Table 2**).

A small RCT in 16 participants with BD I and II minimally symptomatic reported that compared to placebo (n=10) galantamine (n=6) showed no significant effect of galantamine on depression, mania, cognitive performance, and global functioning (assessed with GAF) (Ghaemi et al., 2009). Similar findings about depression, mania and cognitive performance were shown by Iosifescu et al. in an open-label trial comparing 11 patients with BD vs. 10 age- and sex-matched healthy controls. In this trial, 2 participants treated with galantamine stopped the treatment due to side effects (Iosifescu et al., 2009). Finally, in a small case series of 4 BD I-II patients, contrasting findings about cognitive status were found, since 2 patients each either showed significant or no improvement compared to baseline. However, 2 patients reported side effects during the follow-up period (Schrauwen and Ghaemi, 2006).

Memantine

Among 4 studies with memantine (**Table 2**), one RCT of 24 patients with bipolar depression showed that compared to placebo (n=12) treatment with memantine (n=12) significantly improved response and remission rate in 8 patients compared to 4 in the placebo group, although no significant between group difference was reported using the Hamilton Depression Rating Scale (HDRS). No other significant results regarding mania or global functioning were observed. Finally, no significant increased risk of side effect was noted in the treated vs. placebo group (Anand et al., 2012). Conversely, in a large RCT of 157 patients with BD-II in a depressive episode, Lee et al. reported that memantine did not have any significant effect on depression or mania in 81

participants treated with memantine vs. 76 controls taking placebo. Surprisingly, side effects were reported only in the placebo group with one being severe (suicide attempt) (Lee et al., 2014). Also, an open label trial in 40 patients with treatment resistant BD and any type of polarity showed that memantine improved global functioning in the 80% of participants, i.e., 47.5% very much, 25% much and 7.5% minimally improved. During the study, 4 participants discontinued memantine, 1 for side effects (Koukopoulos et al., 2012). Finally, an open label study (Keck et al., 2009) with no control group including manic and mixed patients, suggested a role of memantine in reducing manic symptoms, but results were limited by several limitations acknowledged by authors.

Rivastigmine

No study was found investigating the use of rivastigmine in BD.

INSERT TABLE 3 HERE

Evidence synthesis

Table 3 summarizes the information available about the use of AceI and memantine in BD.

For donepezil there was a strong evidence of no effect on mania and psychosis and a low evidence of no effect on depression and cognitive performance.

Taken together data about galantamine, results suggest strong evidence of no effect on mania, moderate evidence of no effect on depression, low evidence of no effect on global functioning, conflicting evidence on California Verbal Learning Test (CVLT), moderate evidence of no effect on Wisconsin Card Sorting Test (WCST), and no evidence on psychotic symptoms. Finally, conflicting evidence emerged supporting the use of memantine on mania, depression, and global functioning, strong evidence of no effect on mania, and no evidence for effects on cognitive performance and psychotic symptoms.

DISCUSSION

In this systematic review, we summarized the current evidence about the use of AceI and memantine in patients with BD. Twelve studies including 275 patients (102 treated with donepezil, 21 with galantamine and 152 with memantine) with 147 controls (137 treated with placebo and 10 healthy controls) yielded inconclusive findings about the utility of memantine in the short- or medium-term treatment of BD, or where the evidence was stronger, AceI did not seem to improve or worsen any clinical outcome in patients with BD..

Donepezil is an AceI that has been shown to significantly improve cognitive function in patients with Alzheimer's disease (Birks, 2006). Its mechanism is linked to an increase in acetylcholine concentrations in the brain that have beneficial effects on cognition. As the same mechanism seems to be important to decrease manic symptoms a potential role of donepezil in BD was suggested (Higley and Picciotto, 2014). However, the available data from our systematic review suggest no effect on mania, psychosis or depression. These unexpected findings could be explained by several hypotheses. First, it has been reported that donepezil could paradoxically increase manic symptoms (rebound mania) particularly in subjects without mood stabilizers and during the first days of treatment (Benazzi, 1999). Therefore, it is possible that some subjects initially experiencing these symptoms left the study or that the anti-manic effect of donepezil was counterbalanced by this initial activation. Secondly, the effect of donepezil on cognition in people with other concomitant psychiatric co-morbidities is still debated, mainly due to the low quality of the studies investigating this topic (Stip et al., 2007). However, the global impression is that AceI work less well in the presence of psychiatric diseases with a neurodegenerative basis (Singh et al., 2012; Stip et al., 2007) opening the question if these drugs are really useful in people with an already established severe psychiatric condition. Finally, several methodological issues in the selected studies could also explain the negative findings, including the availability of only few and small RCTs, and the high heterogeneity of the included participants and outcomes. Donepezil was associated with a relatively high incidence of AEs, mainly gastrointestinal and mild to moderate in nature. However, Evins et

al. reported a serious adverse event (ultrapid cycling) as well as poor compliance in patients treated with donepezil due to side effects (Ae et al., 2006). These results were substantially confirmed by the second RCT with donepezil showing a higher incidence of adverse effects in individuals treated with donepezil vs. placebo (Chen et al., 2013).

Conversely, data about galantamine seem to be more consistent compared to donepezil. Galantamine has a similar mechanism of action compared to donepezil, enhancing acetylcholine levels in the brain. In addition, donepezil modulates nicotinic receptors influencing dopamine and glutamate balance. This second pathway could be important in mnemonic functioning. Altogether, galantamine does not seem to improve any of the studied outcomes, with strong evidence regarding mania, and moderate evidence for no effect on cognition (WCST) and depression. However, these findings should be considered preliminary. In an open label trial, Iosifescu et al. found that cognitive performance was more impaired in BD patients than age-matched healthy controls and that the treatment with galantamine seemed to partially reverse this abnormality in the BD patients (Iosifescu et al., 2009). Conversely, Ghaemi et al. confirmed a substantial improvement at follow-up in some cognitive measures, but not versus the placebo group, possibly due to the small sample included in this RCT (Ghaemi et al., 2009). Therefore, further, larger studies are needed to investigate whether galantamine could be used for the treatment of cognitive impairment in BD and which domains could benefit the most (with different results for CVLT vs WCST). Nevertheless, galantamine did not significantly improve depression or mania. However, this lack of effect could be attributable to the inclusion of BD patients without active manic or depressive symptoms at baseline in almost all of the studies included. Therefore, trials including patients with an active manic or depressive episode could better clarify the role of galantamine in the acute phases of BD (Schrauwen and Ghaemi, 2006). Moreover, in contrast with cross-sectional reports (Budde and Schulze, 2014), other authors (Strejilevich et al., 2015) recently suggested that evidence of a progressively deteriorating course of cognitive function over time in BD is inconsistent. Regarding safety and tolerability, side effects were reported in two of the three included studies. In one of

these studies, two out of 11 patients stopped the treatment due to adverse effects (Iosifescu et al., 2009) and in the other study, half (2 out of 4) of the patients on galantamine developed an adverse effect (Schrauwen and Ghaemi, 2006). Unfortunately, comparative data with the placebo group were not available since the only included RCT did not report detailed adverse effect data with galantamine (Ghaemi et al., 2009).

Regarding memantine, we found conflicting evidence about its effect on mania, depressive and psychotic symptoms. Unfortunately no data were available about cognition. Memantine is commonly used in moderate forms of cognitive impairment in Alzheimer's disease (Birks, 2006). Its mechanism could be of interest in disorders other than dementia since its neuroprotective effect seems to be stronger than donepezil or galantamine. Moreover memantine acts as a non-competitive NMDA antagonist, with suggested antidepressant and mood stabilizing effects (Lee et al., 2013). Its mechanism of action on NMDA receptors is shared with ketamine, which in turn showed antidepressant properties, but which can also have strong dose-dependent dissociative properties and potential neurotoxic effects (Iadarola et al., 2015). Conversely, these side effects do not occur with memantine, which has a safer profile. Moreover memantine seems to block the development of upregulation of dopamine receptors caused by antidepressants, and the consequent desensitization associated with the depressive-like behavior in animal studies, suggesting a role in the treatment or prevention of mania (Serra et al., 2014c). However, our results indicate that conflicting evidence is available about memantine for manic symptoms, while further studies are needed for depression, psychosis and cognition. These results from randomized controlled trials are in contrast with previous reviews (Sani et al., 2012; Serra et al., 2014c) and several case reports about memantine in BD, which each suggested efficacy of memantine in BD (De Chiara et al.; Serra et al., 2013, 2014a, 2014b). However, the uncontrolled and isolated nature of these reports is at best hypothesis-generating. Furthermore, since all studies focused on short- or medium-term treatment, we were unable to evaluate the effect of AchI or memantine on relapse prevention, for which only case reports (Sani et al., 2012; Serra et al., 2014c) and one mirror image study (Serra et al., 2015) exist,

underscoring the need for additional controlled studies. Additionally, we could not include a 3-year naturalistic trial suggesting memantine's efficacy for manic symptoms, since it included patients underwent ECT, which we chose to exclude from the evaluated studies (Serra et al., 2015). Further, the need of more studies investigating memantine in mania is highlighted by the fact that participants were mainly depressed at baseline, with a low score on scales assessing mania, which does not allow a meaningful assessment of the anti-manic properties of memantine. Nevertheless, memantine seemed to be associated with less adverse effects than AceI. Anand et al. reported no significant differences between treated and placebo group (Anand et al., 2012), while Lee et al. reported the presence of adverse effects (including one suicide attempt) in the placebo group only (Lee et al., 2014).

Limitations

The findings of our systematic review should be considered within its clear limitations. First, we were not able to meta-analyze any of the outcomes due to the lack of RCTs and paucity and heterogeneity of outcome measures utilized. Second, the included studies were generally small and of short duration. The latter is a crucial limitation, precluding any evidence synthesis about the role of AceI and memantine in the maintenance treatment and relapse prevention in BD. Third, the patients were very heterogeneous across and, even, within studies, which could further explain the observed lack of efficacy and which should stimulate the search for efficacy in particular subgroups of patients. Fourth, data on each of the medication classes across the different phases of bipolar disorder are lacking precluding any conclusions. Finally, no data were published on rivastigmine; however, case reports seemed to be in agreement with the data about lack of effect of AceI in BD (Pavlis et al., 2007; Tseng and Tzeng, 2012).

In conclusion, little but converging evidence of no efficacy is available for AceI in BD, and conflicting evidence is available on a broad range of outcomes for memantine. However, since high

quality studies in patients enriched for the respective outcomes of interest are very scarce, larger RCTs seem to be necessary to more conclusively evaluate the effectiveness and safety of Acel and memantine in patients with BD who are either manic, depressed or euthymic, and longer-term studies are needed to assess their efficacy for maintenance treatment and relapse prevention in BD.

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Conflict of interest

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Authors' role

Data interpretation and analysis: Stubbs, Zaninotto, Veronese, Luchini. Draft of the manuscript: Solmi, Lu, Correll. Literature search: Veronese, Solmi. Data extraction: Veronese, Luchini. All the Authors approved the final version of the article.

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Table 1. Characteristics of identified Studies Investigating Anti-dementia Drugs in Bipolar Disorder

Study/ Year (Country)	Design	Setting	Partici- pants	Treatment (dose, mg/day)	Duration (weeks)	Inclusion criteria	Exclusion criteria	Other psychiatric co- morbidity	% with psychosis	Age, mean±SD (range)	Females (%)
<i>Donepezil (DZP)</i>											
Burt, 1999 (USA)	Case series; retrospective	Out-patients	11	DZP (5 mg for the first 4 weeks; after: 10 mg)	4.5 (3 days-6 weeks)	BD I; 4 manic, 5 mixed, 1 hypomanic, 1 depressive episode. Resistant to or intolerant of at least two prior approved treatments for bipolar disorder; partial responders or nonresponders to lithium	na	81.8% had previous psychotic mood episode; 63.6% alcohol or other drugs dependence	0% (at the time of enrolment)	39.2 (20-54)	63.6%
Chen, 2013 (China)	RCT	In-patients	15 in the treated and 15 in placebo group	DZP (5 mg for the 1 st week and increased to 10 mg) vs. Placebo + Lithium in both groups	4	BD I with acute manic episodes	Allergy to lithium or donepezil; history of suicide attempts; active substance abuse in the past 2 weeks or dependence in the past 2 months; other physical comorbidities; pregnancy/lactation; other anticholinergic drugs	na	na	33.9±15.8 (treated) vs. 34.6±11.0 (placebo)	40.0% in both groups
Evins, 2006 (USA)	RCT	Out-patients	6 in the treated and 5 in the placebo	DZP (5 mg for 4 weeks and increased to	6	Adult; Resistant BD I, all manic, with a YMRS≥15	Any drug abuse in the past 2 weeks; substance dependence in the	0%	na	42.2±16.3 (treated) vs. 36.6±11.2	66.7% in the treated vs. 100%

Group	Intervention	Comparison	Number of participants	Duration	Outcomes
10 mg in the last 2 weeks) vs. Placebo	DZP (5 mg for the first 4 weeks; after: 10 mg, but one patient remained on 5 mg)	12	Age 60 yrs or older; BD I-II; clinical euthymia (HRSD-17 and YMRS < 10); corrected visual ability to read newspaper headlines and hearing capacity adequate to respond to a raised conversational voice; cognitive dysfunction	na	other psychiatric or medical disorders; diseases requiring use of anticholinergic medications or cholinomimetics; pregnancy or lactation
(5 mg; up to 10 in non-	DZP	47	BD I 12%, BD II 74.2%, NOS 13.8%	na	

Study/ Year (Country)	Design	Setting	Partici- pants	Treatment (dose, mg/day)	Duration (weeks)	Inclusion criteria	Exclusion criteria	Other psychiatric co- morbidity	% with psychosis	Age, mean±SD (range)	Females (%)
Sub-total DZP (means, SDs and percentages are weighted with n values)	RCTs: (N=2); naturalistic case-series (N=1); open-label; (N=1); case series retrospective; (N=1)	out-patients (N=4); in-patients (N=1)	Treated with DZP: 102; Controls: 20 (placebo);	Start dose: 5 mg, target dose: 10 mg (N=4), 5-10 mg (n=1)	All studies: 20 weeks; RCT: 5 weeks; Other: 21 weeks	BD I all phases (N=1), BD I manic (N=1), resistant BD I manic (N=1), BD I or II euthymic (N=2)	suicide attempts, cholinergic medications, medical condition and substance abuse (N=3), na (N=2), psychiatric comorbidity (N=1), dementia (N=1)	na (N=3); Psychotic mood episode: 81.8% (N=1), ; Alcohol or other drugs dependence: 63.6% (N=1), 0% (N=1)	na (N=3); 0% (N=2),	Treated: 44.7±17.2 years; Controls: 35.2±10.8 years	Treated: 61.8%; Controls: 57.1%
Galantamine (GAL)											
Ghaemi, 2009 (USA)	RCT	Out-patients	6 in the treated; 10 in the placebo group	GAL SR (8 mg/d for the first 4 weeks; 16 mg/d for the following; 24 mg/d for the last 4 weeks) vs. Placebo Mean (SD)=19.4 (6.8)	12	Age 18-60 years; BD I 60%, BD II 40%, minimally symptomatic, subjective self- reports of cognitive impairment; MRS≤15; MADRS≤10; MMSE≥ 2	Substance abuse in the previous month; psychiatric or medical conditions; active suicidal ideation.	0%	na	46.9±10.9 (treated) vs. 46.3±9.8 (placebo)	54% in the treated group vs. 33% in the placebo group
Iosifescu, 2009 (USA)	Open-label with controls	Out-patient	11 completers BP I-II; 10 age-and sex matched healthy controls	GAL-ER (8 mg/day for the first 4 weeks; 5-8 weeks: up to 16 mg/day; 8-16 weeks: up to 24mg/day) Range 8-24	16	Age 18-65; DSM-IV BD I 75%, BD II 25%, all euthymic in remission; HAM-D 17 and YMRS <10; subjective cognitive deficit	Suicidal ideation; pregnancy; medical conditions; psychosis; mood disorders with psychotic features; active smoking; drugs/alcohol dependence; ECT;	0%	0%	40.7±11.9 (treated) vs. 38.9±10.1 (healthy controls)	30% in both groups

[illegible]

Study/ Year (Country)	Design	Setting	Partici- pants	Treatment (dose, mg/day)	Duration (weeks)	Inclusion criteria	Exclusion criteria	Other psychiatric co- morbidity	% with psychosis	Age, mean±SD (range)	Females (%)
Anand, 2012 (USA)	RCT	Out-patients	12 in both groups	MEM (5 mg/d 1 st week and increasing 5 mg/d each week until 20 mg/d) vs. Placebo range: 5-20 mg/d	8	Age 18–65; DSM-IV-TR BD I (62%) BD II (38%), current depressive episode; lamotrigine inadequate- response; stable dose of other antidepressants, mood stabilizers, or any other psychotropic drugs, if any, for the past four weeks	Suicidal or homicidal risk; medical conditions; pregnancy, planning to be pregnant, or not using adequate contraception; substance dependence within six months prior to the start of the study; any medication with significant known adverse interaction with either mementine or lamotrigine; schizophrenia or schizoaffective disorder	na	0%	38±15 (treated) vs. 41±14 (placebo)	64.3% in the treated vs. 53.3% in the placebo group
Keck, 2009 (USA)	Open-label, pilot, multicenter	In-patients	19 All BD I	MEM (20-40 mg/day)	3	BD type I (manic or mixed episode); YMRS>20; 18-65	Cognitive disorders; psychotic disorders; axis II DSM-IV diagnoses; HIV +; medical conditions; suicidal ideation; other psychotropic drugs	ADHD; OCD; anxiety disorders; substances abuse	0%	41.2±12.0 (18-66)	54.3%
Koukopoulos, 2012 (Italy)	Naturalistic open-label	Out-patient	40	MEM (10-30 mg/day)	48	>18 ys; BD I (52.5%), or BD II (47.5%), rapid cyclers (47.5%), long cycles (22.5%),	na	na	47.5%	49.0±16.0	75%

Study/ Year (Country)	Design	Setting	Partici- pants	Treatment (dose, mg/day)	Duration (weeks)	Inclusion criteria	Exclusion criteria	Other psychiatric co- morbidityes	% with psychosis	Age, mean±SD (range)	Females (%)
						resistant for at least 4 years to common medications, CGI-BP>5					
Lee, 2014 (Taiwan)	RCT	Out- and in- patients	81 in the treated vs. 76 in the placebo group	MEM (5 mg/d) vs. placebo + valproate	12	BD type II, depressed mood.	Other psychiatric diseases; drugs dependence; taking MEM 1 week before the beginning of the study	0%	na	32.4±11.8 (treated) vs. 29.8±10.6 (placebo)	48.1% in the treated vs. 61.8% in the placebo group
Sub-total MEM (means, SDs and percentages are weighted with n values)	RCTs: N=2); open-label, pilot, multicentre (N=1); naturalistic open-label (N=1)	out- patients(N=2); 1 in-patients (N=1); both in- and out- patients(N=1)	Treated: 152; Controls: 88 (placebo)	5 mg/d 1 st week and increasing 5 mg/d each week until 20 mg/d, range 5-20 (N=1); range: 20-40 mg/d (N=1); range: 10-30 mg/d (N=1), 5 mg/d + valproate (N=1)	All studies: 17.8 weeks; RCTs: 10 weeks; Other: 25.5 weeks	BD I or BD II, current depressive episode, BD II depressed mood (N=1); BD I manic or mixed episode (N=1); BD I or BD II rapid cyclers, long cyclers (N=1)	Substance abuse, Psychiatric condition, interacting drugs (N=3); plus suicidal ideation (N=2); or plus HIV and cognitive decline (N=1), na (N=1)	na (N=2); 0% (N=1); ADHD, OCD, anxiety (N=1)	0% (N=2); 47.5% (N=1); na (N=1), years	Treated: 38.3±15.0 years; Controls: 31.3±11.7 years	Treated: 56.6% Controls: 60.2%
Total (means, SDs and percentages are weighted with n values)	RCTs: (N=5); Other designs: (N=7)	Out-patients: (N=8); In-patients (N=4); Both: (N=1)	Treated: 284; Controls: 128 (118 with placebo)	5 studies; Start dose: 5 mg/d, target dose: 10 mg/d (N=4), 5-10 mg/d (n=1) GAL: 4 studies;	All studies: 20 weeks; RCTs: 9.7 weeks; Other: 28.2 weeks	BD I or II euthymic (N=3); BD I all phases (N=1); BD I manic (N=1); resistant BD I manic (N=1); BD I, manic or hypomanic	Main criteria: na (N=6); 0% (N=4); Substance abuse (N=8); interacting drugs (N=7); plus suicidal ideation (N=7); other psychiatric condition (N=7); na (N=4).	na (N=6); 0% (N=4); ADHD, OCD, anxiety (N=1); psychotic mood episode: 81.8%	na (N=10); 0% (N=3);	Treated: 41.8±16.1 years Controls: 36.1±13.9 years	Treated: 57.5%; Controls: 55.0%

Study/ Year (Country)	Design	Setting	Partici- pants	Treatment (dose, mg/day)	Duration (weeks)	Inclusion criteria	Exclusion criteria	Other psychiatric co- morbidities	% with psychosis	Age, mean±SD (range)	Females (%)
				<i>Weeks 1-4</i> 8 mg/d, <i>weeks 5-8:</i> 16 mg/d, <i>weeks 9-12:</i> 24 mg/d (N=2), mean (SD)=18 (12) mg/d (N=1), 19.4 (6.8) mg/d (N=1), range: 8-24 mg/d. MEM: 4 studies;5 mg/d 1 st week and increasing 5 mg/d each week until 20 mg/d, range: 5-20 mg/d (N=1), 20-40 mg/d (N=1), 10-30 mg/d (N=1), 5 mg/d + valproate (N=1)		(N=1); BD I manic or mixed episode (N=1), BD I or II minimally symptomatic with subjective cognitive impairment (N=1); BD I or BD II, current depressive episode, BD II depressed mood (N=1); BD I or BD II rapid cyclers, long cyclers, phase na (N=1)	<i>ECT (N=1); medical condition (N=3) and substance abuse (N=3); HIV and cognitive decline (N=2); psychiatric comorbidity (N=1)</i>	(N=1); alcohol or other drugs dependence 63.6% (N=1)			

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder; BD: bipolar disorder; BPRS: Brief Psychiatric Rating Scale; CVLT-II: California Verbal Learning Test; DKEFS: Delis-Kaplan Executive Functioning System; DZP: donepezil; ECT: Electroconvulsive Therapy; GAF: global assessment of functioning scale; CGI: clinical Global Impression; HAM-D: Hamilton Depression Scale; GAL: galantamine; IADL: instrumental activities of daily living; LIFE-RIFT: the Life Chart Methodology, and the Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool; MADRS: Montgomery Asberg Depression Rating Scale; MEM: memantine; MMSE: mini-mental state examination;

MRS: Mania Rating Scale; N: number of studies; na: not available; OCD: obsessive compulsive disorders; YMRS: Young Mania Rating Scale; WCST: Wisconsin Card Sorting Test.

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Table 2. Main Efficacy and Safety Outcomes in Studies Investigating Anti-dementia Drugs in Bipolar Disorder

Study/ Year (Country)	Participants Characteristics	Depression	Mania	Global	Cognitive	Psychosis	Side effects	Jadad score
<i>Donepezil</i>								
Burt, 1999 (USA)	11 patients (4 manic, 5 mixed, 1 hypomanic, 1 depressed); All responders at 5, no one at 10 mg	na	na	Mean decrease of CGI-S of 1.46 points; Mean GAF increase of 11.5 points	na	na	5 patients: 2 insomnia, 2 nausea, 2 diarrhea, 1 sedation	0
Chen, 2013 (China)	All manic. (15 DZP vs. 15 PLB)	na	YMRS: -18.6±3.2 (DZP) vs. -25.3±5.5 (PLB) P=0.16	na	na	BPRS negative: -1.2±0.3 (DZP) vs. -1.8±0.6 (PLB) P=0.32; BPRS positive: -5.1±1.0 (DZP) vs. -6.6±1.7 (PLB) P=0.31; BPRS total: -12.6±2.7 (DZP) vs. -13.9±12.2 (PLB) P=0.75	19 mild to moderate AE (DZP) vs. 7 mild to moderate AE (PLB)	5
Evins, 2006 (USA)	All manic. (6 DZP vs. 5 PLB)	No differences at follow-up about HDRS between groups.	No clinical response (reduction of YMRS >30% compared to baseline) in DZP; 60% clinical response in PLB group (p=0.06)	na	na	No differences at follow-up about BPRS between groups	33 AE in DZP group vs. 7 in PLB; 4/6 of DZP group discontinued the treatment for AE vs. 0/5 in PLB group; 1 serious AE in DZP group (ultrapid cycling)	4
Gildengers, 2008 (USA)	12 older BP patients with cognitive	na	na	na	No significant effects were observed in	na	1 nausea; 2 manic activation.	1

Study/ Year (Country)	Participants Characteristics	Depression	Mania	Global	Cognitive	Psychosis	Side effects	Jadad score
	dysfunction				cognitive performance assessed with digit-span (attention); Trails A+ digit symbol (information processing speed); Trails B+ STROOP (executive function)			
Kelly, 2007 (USA)	58BD patients	na	na	CGI-I BD I: 57% worsened, no improvement in this group; BD II: improvement of 1.8±0.8 vs. baseline; NOS: 2.0±0.8 vs. baseline <i>Galantamine</i> CGI: -0.5±1.0 (GAL) vs. -0.6±0.7 (PLB) (p=0.002); GAF: 3.0±11.2 (GAL) vs. -3.2±10.4 (PLB)	BD I: 0% improved; BD II: 81% improved; NOS: 50% improved.	na	Nine treatments were stopped because of AE; Seven stopped DZP for AE	0
Ghaemi, 2009 (USA)	16 BD I-II (6 GAL vs. 10 PLB)	MADRS: -4.3±10.0 (GAL) vs. -3.5±5.5 (PLB) (p=0.78)	MRS: -2.2±5.1 (GAL) vs. -0.5±4.1 (PLB) (p=0.31)		CVLT learning: 10.7±5.1 (GAL) vs. 1.5±8.0 (PLB) (p=0.32); WCST: -1.8±2.1 (GAL) vs. 0.9±2.0 (PLB)	na	na	5

Study/ Year (Country)	Participants Characteristics	Depression	Mania	Global	Cognitive	Psychosis	Side effects	Jadad score
Iosifescu, 2009 (USA)	11 BD vs. 10 HCs	HDRS-17: 2.9±4.1 (GAL) vs. 0.9±1.7 (HCs) (p=0.20)	YMRS: 2.1±4.4 (GAL) vs. 1.6±4.3 (HCs) (p=0.82)	na	(p=0.13) CVLT learning: 7.0±7.4 (GAL) vs. 0.8±3.2 (HCs) (p=0.03); WCST: -3.0±4.9 (GAL) vs. -0.79±8.3 (HCs) (p=0.48) CGI-I: 2 unchanged; 1 very much improved; 1 much improved	na	2 stopped the treatment in GAL group.	2
Schrauwen, 2006 (USA)	4 BD I-II	na	na	na	2 unchanged; 1 very much improved; 1 much improved	na	2/4 (=50%) reported AEs	0
Anand, 2012 (USA)	All major depressive phase of BD. (14 MEM vs. 15 PLB).	HDRS: Both groups significantly improved vs. baseline (p<0.0001 for both) without significant differences between groups at final follow- up (p=0.59); MEM group had a significant higher response rate at week 4	YMRS: No significant differences between groups at follow-up (p=0.56)	CGI-I: No significant differences between groups at follow-up (p=0.91); CGI-S: No significant differences between groups at follow-up (p=0.12).	na	na	No significant differences of AE between groups; 9/14 stopped the treatment with MEM before the ending	5

Study/ Year (Country)	Participants Characteristics	Depression	Mania	Global	Cognitive	Psychosis	Side effects	Jadad score
		(p=0.004) and remission rate at week 6 (p=0.004) than PLB group						
Keck, 2009 (USA)	33 manic or mixed BD I patients. Three cohorts: 1: 20-30 mg MEM 2: 30-40 mg MEM 3: 30-50 mg MEM	MADRS: Changes in all cohorts (p=NA)	YMRS: Greatest change at lowest dose of MEM (20 mg); Response= 50% reduction in YMRS with lowest and intermediate dose of MEM	CGI-S: Changes in all cohorts (p=NA); CGI-I: Changes in all cohorts (p=NA)	na	PANSS: Changes in all cohorts (p=NA)	19 (54.3%) with mild to moderate AE	1
Koukopoulos, 2012 (Italy)	40 BD patients.	na	na	CGI-BP: (6 months) 47.5% very much improved; 25% much improved; 7.5% minimally improved; 20% unchanged	na	na	4/40 discontinued MEM, 1/40 for AE	1
Lee, 2014 (Taiwan)	137 depressed BD II (81 MEM vs. 76 PLB)	HDRS: -43.8±61.4% (MEM) vs. -53.1±30.1% (PLB) (p=0.24)	YMRS: -26.5±0.8% (MEM) vs. -30.2±0.6% (PLB) (p=0.74)	na	na	na	AEs only in PLB group: 1 hair loss, 1 dizziness, 1 suicide attempt	3

Abbreviations: AE: Adverse Event; BD: Bipolar Disorder; BPRS: Brief Psychiatric Rating Scale; CGI-BP: Clinical Global Impression-Bipolar Illness; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; CVLT: California Verbal Learning Test-Second Edition; DZP: Donepezil; GAF: Global Assessment of Functioning; GAL: Galantamine; HC: healthy control; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery Asberg Depression Rating; MEM: Memantine; MRS: Mania Rating Scale; na: not available; PANSS: Positive and Negative Syndrome Scale; YMRS: Young Mania Rating Scale; WCST: Wisconsin Card Sorting Test.

Table 3. Best Evidence Synthesis.

Drug	Depression	Mania	Global	Cognitive	Psychosis
Studies (quality) (DZP)	Evins (high), 2006: =	Evins (high), 2006: = Chen (high), 2013: =	Burt (no), 1999: ?	Gildengers (low), 2008: = Kelly, 2007 (no): ?	Chen (high), 2013: = Evins (high), 2006: =
Evidence level	Low evidence no effect	Strong evidence no effect	No evidence	No evidence	Strong evidence no effect
Studies (quality) (GAL)	Ghaemi (high), 2009: = Iosifescu (medium), 2009: =	Ghaemi (high), 2009: = Iosifescu (medium), 2009: =	Ghaemi (high), 2009: =	Ghaemi (high), 2009: CVLT =, WCST = Iosifescu (medium), 2009: CVLT +, WCST =	No studies available
Evidence level	Moderate evidence no effect	Moderate evidence no effect	Low evidence no effect	Conflicting evidence CVLT, Moderate evidence no effect WCST	No evidence
Studies (quality) (MEM)	Anand (high), 2012: + Keck (low), 2009: ? Lee (high), 2014: =	Anand (high), 2012: = Keck (low), 2009: ?/+ Lee (high), 2014: =	Anand (high), 2012: = Keck (low), 2009: ? Koukopolous (low), 2012: +	No studies available	Keck (low), 2009: ?
Evidence level	Conflicting evidence	Conflicting evidence	Conflicting evidence	No evidence	No evidence

Notes:

Symbols:

- + : significant improvement of drug vs. placebo (RCTs) or vs. control group (open label with control group) or significant improvement at follow-up vs. baseline (other designs);
- = : no significant difference between treated vs. placebo (RCTs) or vs. control group (open label with control group) or significant improvement at follow-up vs. baseline (other designs);
- : significant improvement of placebo vs. drug (RCTs) or control group vs. drug (open label with control group) or significant worsening at follow-up vs. baseline (other designs).
- ? : the study reported data without declaring if significant differences exist.

Quality of the studies:

The quality of involved studies in this systematic review was evaluated using Jadad scale [15]. This scale includes randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). The overall score of a study according to this scale varies among 0–5, with greater scores as a measure of better quality [16]. Studies with Jadad scale of 0, 1, 2 and ≥ 3 were considered as no, low-, medium- and high-quality, respectively.

Evidence level:

Strong evidence: 2 high-quality studies in agreement about an outcome;
 Moderate evidence: 1 high-quality + 1 medium quality, or 3 medium-quality studies in agreement; Low evidence: 1 high quality, or 2 medium-quality, or 3 low studies in agreement;
 No evidence: 1 medium-quality study, or < 3 low quality studies in agreement, or any number of no quality studies in agreement, or no studies at all;
 Conflicting evidence: contrasting findings of low to strong evidence among studies.

FIGURE LEGENDS**Figure 1.** PRISMA flow-chart**Highlights**

- Only few and small studies evaluated donepezil, galantamine or memantine in bipolar disorder.
- Evidence points to no effect of donepezil and galantamine for all aspects of bipolar disorder.
- For memantine, efficacy results are conflicting regarding depression and global functioning.
- There is currently no support for using donepezil, galantamine or memantine in bipolar disorder.

Fig. 1